INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB03/02971

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 39/395
US CL : 424/143.1, 145.1, 152.1, 153.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/143.1, 145.1, 152.1, 153.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92/22324 A1 (XOMA CORPORATION) 23 December 1992 (23.12.92), see full text, especially abstract.	1-19
Y	US 6,448,054 B1 (POZNANSKY et al) 10 September 2002(10.09.2002), see abstract and claims, especially col. 4, lines 11-20.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 December 2003 (29.12.2003)	02 JUN 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Marianne Seidel Telephone No. 571/272-1600

Form PCT/ISA/210 (second sheet) (July 1998)

Continuation of B. FIELDS SEARCHED Item 3:
CAS/STN ONLINE, CAPLUS, USAPTFUL
search terms: anti-cytokine, antibody, F(ab)'2, immune disease, treatment, psoriasis, arthritis, interleukins(IL-1, IL-6 and IL-12)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2099.008PC00	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB03/02971	International filing date *(day/month/year)* 25 July 2003 (25.07.2003)	Priority date *(day/month/year)*
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 39/395 and US Cl.: 424/143.1, 145.1, 152.1, 153.1		
Applicant LOPEZ DE SILANES, JUAN		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25 February 2005 (25.02.2005)	14 April 2005 (14.04.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/ US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Vickie Kim Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB03/02971

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed.

☒ the description:
pages 1-25 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages NONE, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages 26-31, filed with the demand
pages NONE, filed with the letter of _____.

☐ the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language English which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☒ the claims, Nos. 1-19

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/IB03/02971

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims 20-61	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 20-61	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 20-61	YES
	Claims NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 20-61 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the claimed invention (i.e. medical utility of anti-cytokine F(ab')2 antibody fragments in the treatment of cytokine-mediated immune reaction (e.g. psoriasis or rheumatoid arthritis).
WO92/22324 teaches anti-cytokine F(ab')2 antibody fragments and its therapeutic uses and diagnostic uses (i.e. diagnosis of tumor metastases (e.g. tumor imaging) or improving delivery of therapeutic agents). However, it fails to teach its use in the treatment of cytokine-mediated immune reaction (e.g. psoriasis). Thus, all the claimed invention is considered to be novel and meet the criteria set out in PCT Article 33(2)-(3).

Claims 20-61 meet the criteria set out in PCT Article 33(4), and thus the claimed invention improves industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------

NONE

WHAT IS CLAIMED IS: 2e.

Claims 1-19. (Cancelled).

20. A method for treating a cytokine-mediated immune reaction in a patient in need thereof comprising, topically administering to said patient an effective amount of anti-cytokine $F(ab')_2$ antibody fragments.

21. The method of claim 20, wherein said cytokine-mediated immune reaction comprises a T cell-mediated inflammatory disease.

22. The method of claim 21, wherein said T cell-mediated inflammatory disease comprises psoriasis vulgaris.

23. The method of claim 20, wherein said cytokine-mediated immune reaction comprises chronic inflammatory disease.

24. The method of claim 20, wherein said cytokine-mediated immune reaction comprises acute inflammatory disease.

25. The method of claim 23, wherein said chronic inflammatory disease comprises rheumatoid arthritis.

26. The method of claim 23, wherein said chronic inflammatory disease comprises an ophthalmic inflammatory disorder.

AMENDED SHEET

27. The method of claim 24, wherein said acute inflammatory disease comprises an ophthalmic inflammatory disorder.

28. The method claim 26 or 27, wherein said ophthalmic inflammatory disorder is selected from the group consisting of: keratitis, uveitis, blepharitis, dry eye and inflammation related to infection.

29. The method of claim 20, wherein said cytokine-mediated immune reaction is acute inflammatory disease.

30. The method of claim 20, wherein said cytokine-mediated immune reaction comprises septic shock.

31. The method of claim 20, wherein said cytokine-mediated immune reaction comprises rejection of a prosthetic or tissue transplant.

32. The method of claim 31, wherein said tissue transplant rejection comprises acute corneal transplant rejection.

33. The method of any one of claims 20 to 32, wherein said anti-cytokine $F(ab')_2$ antibody fragments are applied in combination with a dermatologically or ophthalmically acceptable carrier.

34. The method of any one of claims 20 to 32, wherein said anti-cytokine $F(ab')_2$ antibody fragments are substantially free of albumin, whole antibodies, pyrogens and/or viruses.

35. The method of claim 34, wherein said anti-cytokine $F(ab')_2$ antibody fragments are administered in combination with a dermatologically or ophthalmically acceptable carrier.

36. The method of any one of claims 20 to 35, wherein said cytokine is alpha tumor necrosis factor (TNF-α)

37. The method of any one of claims 20 to 35, wherein said cytokine is beta tumor necrosis factor (TNF-β).

38. The method of any one of claims 20 to 35, wherein said cytokine is an interleukin.

39. The method of claim 38, wherein said interleukin is interleukin-1 (IL-1).

40. The method of claim 38, wherein said interleukin is interleukin-1 alpha (IL-1α).

41. The method of claim 38, wherein said interleukin is interleukin-1 beta (IL-1β).

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42. The method of claim 38, wherein said interleukin is interleukin-2 (IL-2).

43. The method of claim 38, wherein said interleukin is interleukin-6 (IL-6).

44. The method of claim 38, wherein said interleukin is interleukin-12 (IL-12).

45. The method of any one of claims 20 to 35, wherein said cytokine is gamma interferon (IFN-γ).

46. The method of claim 33 or 35, wherein said ophthalmically acceptable carrier comprises one or more components, and wherein said components are selected from the group consisting of: sodium chloride, monobasic sodium phosphate, dibasic sodium phosphate, benzalkonium chloride, methylparaben, propylparaben, tween 80, sodium thiosulphate, sodium metabisulphite, cremophor EL, polyvinilic alcohol, citric acid, boric acid, sodium borate, sodium citrate, glycerine, sodium bisulfite, hydroxypropyl methylcellulose, ethylenediaminetetraacetic acid (EDTA), and reverse osmosis purified water.

47. The use of anti-cytokine $F(ab')_2$ antibody fragments for the manufacture of a medicament for the treatment of a cytokine-mediated immune reaction in a patient in need thereof, wherein said medicament is suitable for topical administration.

48. The use of claim 47, wherein said cytokine is TNF-α.

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IPEA/US 25 FEB 2005

49. The use of claim 47, wherein said cytokine is TNF-β.

50. The use of claim 47, wherein said medicament is suitable for dermatological administration.

51. The use of claim 47, wherein said medicament is suitable for ophthalmic administration.

52. The use of claim 47, wherein said anti-cytokine $F(ab')_2$ antibody fragments are substantially free of albumin, whole antibodies, pyrogens and/or viruses.

53. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises a T cell-mediated inflammatory disease.

54. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises a chronic or acute inflammatory disease.

55. The use of claim 54, wherein said acute or chronic inflammatory disease comprises an ophthalmic inflammatory disorder.

56. The use of claim 55, wherein said ophthalmic inflammatory disorder is selected from the group consisting of: keratitis, uveitis, blepharitis, dry eye and inflammation related to infection.

AMENDED SHEET

57. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises sepsis.

58. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises septic shock.

59. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises rheumatoid arthritis.

60. The use of any one of claims 47 to 52, wherein said cytokine-mediated immune reaction comprises rejection of a prosthetic or tissue transplant.

61. The use of claim 60, wherein said tissue transplant rejection is acute corneal transplant rejection.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:

UNITED STATES PATENT AND TRADEMARK OFFICE
Commissioner for Patents,
P.O.Box 1450
Alexandria VA 22313 -1450
ETATS-UNIS D'AMERIQUE

PCT

INTERNATIONAL APPLICATION STATUS FORM
(IASF)

Date of issue of this IASF:
(the information contained in this IASF reflects the status of the international application as of this date)
09 February 2006 (09.02.2006)

I - INTERNATIONAL APPLICATION		
I-1	International application number:	PCT/IB2003/002971
I-2	International filing date:	25 July 2003 (25.07.2003)
I-3	Earliest priority date:	Not applicable
I-4	Title of the invention:	ADMINISTRATION OF ANTI-CYTOKINE F (AB')2 ANTIBODY FRAGMENTS
I-5	International Patent Classification:	[7] A61K 39/395
I-6	Language of filing:	English
I-7	The State for which the Office acts as a designated Office has been designated in the international application:	Yes
I-7-1	Indication of the State(s) designated in the international application in respect of which the Office acts as a designated Office (only where the designated Office is a regional Office):	Not applicable
I-7-2	The international application has been considered withdrawn in a declaration made by the receiving Office on (date):	Not applicable
I-7-3	The international application or the designation of the State for which the Office acts as a designated Office has been withdrawn by the applicant (date on which withdrawal became effective):	Not applicable
I-7-4	Kind of protection or treatment:	Patent
I-7-4-1	Identification of parent application or parent grant:	Not applicable
I-8	Date of receipt of record copy by the International Bureau:	07 August 2003 (07.08.2003)
I-9	Applicant(s) and/or inventor(s) for the State(s) for which the Office acts as a designated Office	
I-9-1	Applicant and/or inventor	
I-9-1-1	Data currently on record	
I-9-1-1-1	Applicant's and/or inventor's name:	LÓPEZ DE SILANES, Juan
I-9-1-1-2	Address:	Lucerna No. 7 C.P. 06600 Col. Juàrez, Delegación Cuauhtémoc Mexico
I-9-1-1-3	State of nationality:	MX
I-9-1-1-4	State of residence:	MX
I-9-1-1-5	This person is:	Applicant and inventor

I-9-1-2	Data previously on record (in case of a change recorded by the International Bureau under Rule 92*bis*):	No data previously on record available for inclusion in this IASF; any such data is available from the IB.
I-9-1-3	Indication of the State(s) designated in the international application for the purposes of which the person is an applicant and/or inventor (only where the designated Office is a regional Office):	Not applicable
I-9-2	Applicant and/or inventor	
I-9-2-1	Data currently on record	
I-9-2-1-1	Applicant's and/or inventor's name:	PANIAGUA-SOLÍS, Jorge, F.
I-9-2-1-2	Address:	Cerrada de Arenal No. 449 C.P. 14600 Col. Valle Escondido Delegación Tlalpan Mexico
I-9-2-1-3	State of nationality:	MX
I-9-2-1-4	State of residence:	MX
I-9-2-1-5	This person is:	Applicant and inventor
I-9-2-2	Data previously on record (in case of a change recorded by the International Bureau under Rule 92*bis*):	No data previously on record available for inclusion in this IASF; any such data is available from the IB.
I-9-2-3	Indication of the State(s) designated in the international application for the purposes of which the person is an applicant and/or inventor (only where the designated Office is a regional Office):	Not applicable
I-9-3	Applicant and/or inventor	
I-9-3-1	Data currently on record	
I-9-3-1-1	Applicant's and/or inventor's name:	DIAZ-QUIÑONEZ, Alberto
I-9-3-1-2	Address:	Latacunga #755 C.P. 07300 Col. Lindavista Delegación Gustavo A. Madero Mexico
I-9-3-1-3	State of nationality:	MX
I-9-3-1-4	State of residence:	MX
I-9-3-1-5	This person is:	Applicant and inventor
I-9-3-2	Data previously on record (in case of a change recorded by the International Bureau under Rule 92*bis*):	No data previously on record available for inclusion in this IASF; any such data is available from the IB.
I-9-3-3	Indication of the State(s) designated in the international application for the purposes of which the person is an applicant and/or inventor (only where the designated Office is a regional Office):	Not applicable
I-9-4	Applicant and/or inventor	
I-9-4-1	Data currently on record	
I-9-4-1-1	Applicant's and/or inventor's name:	MANCILLA-NAVA, Rita, G.
I-9-4-1-2	Address:	Calzada de Tlalpan No. 4687 C.P. 14050 Col. Toriello Guerra Delegación Tlalpan Mexico
I-9-4-1-3	State of nationality:	MX
I-9-4-1-4	State of residence:	MX
I-9-4-1-5	This person is:	Applicant and inventor
I-9-4-2	Data previously on record (in case of a change recorded by the International Bureau under Rule 92*bis*):	No data previously on record available for inclusion in this IASF; any such data is available from the IB.

I-9-4-3	Indication of the State(s) designated in the international application for the purposes of which the person is an applicant and/or inventor (only where the designated Office is a regional Office):	Not applicable
I-10	The international application contains sequence listings and/or tables filed under Section 801(a) of the Administrative Instructions:	No
I-11	The following declaration(s) referred to in Rule 4.17 made for the purposes of the State(s) for which the Office acts as a designated Office was (were) contained in the international application as filed or received by the International Bureau before the expiration of the time limit under Rule 26*bis*.1:	
I-11-1	Declaration(s) as to the identity of the inventor (Rules 4.17 (i) and 51*bis*.1(a)(i)):	Not applicable
I-11-2	Declaration(s) as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)):	Not applicable
I-11-3	Combined declaration(s) as to the identity of the inventor (Rules 4.17(i) and 51*bis*.1(a)(i)) and the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)) :	Not applicable
I-11-4	Declaration(s) as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application (Rules 4.17(iii) and 51*bis*.1(a)(iii)):	Not applicable
I-11-5	Declaration(s) of inventorship (only for the purposes of the designation of the United States of America) (Rules 4.17 (iv) and 51*bis*.1(a)(iv)):	Not applicable
I-11-6	Declaration(s) as to non-prejudicial disclosures or exceptions to lack of novelty (Rules 4.17(v) and 51*bis*.1(a)(v)):	Not applicable
II - PRIORITY CLAIMS		**Not applicable**
III - INTERNATIONAL SEARCH REPORT		
III-1	International Searching Authority carrying out the international search:	ISA/US
III-2	International search report or declaration under Article 17 (2)(a) received by the International Bureau:	Yes
III-3	Corrected version(s) of the international search report (if any) received by the International Bureau:	Not applicable
IV - REFERENCE TO DEPOSITED BIOLOGICAL MATERIAL		**Not applicable**
V - INTERNATIONAL PUBLICATION		
V-1	International publication number:	WO 2005/009464 (A1)
V-2	International publication date:	03 February 2005 (03.02.2005)
V-3	Language of publication:	English
V-4	Number of figure of drawing published together with the abstract:	Not applicable
V-5	Republication(s) (republication date(s) and reason(s)):	Not applicable
VI - INTERNATIONAL PRELIMINARY EXAMINATION		
VI-1	A demand electing the State(s) for which the Office acts as an elected Office has been received by the International Preliminary Examining Authority (where the elected Office is a regional Office, indication of the State(s) elected in respect of which the Office acts as an elected Office):	Yes 25 February 2005 (25.02.2005)
VI-2	The election was made before/after the expiration of 19 months from the priority date:	Before
VI-3	The election or the demand containing the election of the State(s) for which the Office acts as an elected Office has	Not applicable

	been considered not to have been made or submitted in a declaration made by (the International Bureau/the competent International Preliminary Examining Authority) on (date):	
VI-4	The election or the demand containing the election of the State(s) for which the Office acts as an elected Office has been withdrawn by the applicant (date on which withdrawal became effective being the date of receipt of the notice of withdrawal by the International Bureau) (Rule 90*bis*.4):	Not applicable
VI-5	International Preliminary Examining Authority carrying out international preliminary examination:	IPEA/US
VI-6	International preliminary examination report received by the International Bureau:	Yes
VI-7	Corrected version(s) of the international preliminary examination report (if any) received by the International Bureau:	Information not available for inclusion in this IASF

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Idhir Britel e-mail pct.cor@wipo.int Telephone No. +41 22 338 83 38